OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Viewpoints

Restless Legs Syndrome: Would You Like That with Movements or Without?

Brian B. Koo[1,2*]

[1] Department of Neurology, VA Connecticut Healthcare System, West Haven, Connecticut, USA, [2] Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, USA

Abstract

The restless legs syndrome (RLS) is a common sensorimotor condition that often results in discomfort and sleep disturbance. Diagnosis of RLS is entirely clinical and based upon a patient's description of subjective symptoms, and thus when considering RLS diagnosis non-specificity is a real problem. RLS is associated with periodic limb movements during sleep (PLMS) in up to 90% of RLS sufferers; however, their presence is neither sufficient nor necessary for the diagnosis of RLS. The disease RLS and the motor phenomenon of PLMS share similarities in various areas, which include pathophysiology, pharmacology, genetics, and epidemiology. The purpose of this opinion piece is to outline the many similarities between RLS and PLMS in order to make an argument for the inclusion of PLMS as a supplementary diagnostic criterion of RLS, termed electro-clinical RLS, which would consist of the current clinical RLS diagnosis plus PLMS. This additional criterion could be used in cases where diagnosis is unclear to increase specificity or in research projects where proper diagnosis is desired at the investigational level.

Keywords: restless legs syndrome, RLS, periodic limb movements during sleep, PLMS

Citation: Koo BB. The restless legs syndrome: Would you like that with movements or without? Tremor Other Hyperkinet Mov. 2015; 5. doi: 10.7916/D80P0Z0H

*To whom correspondence should be addressed. E-mail: brian.koo@yale.edu

Editor: Elan D. Louis, Yale University, USA

Received: April 06, 2015 **Accepted:** April 30, 2015 **Published:** July 1, 2015

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The author reports no conflict of interest.

Introduction

The restless legs syndrome (RLS) is a dysesthetic neurologic condition consisting of an inexorable urge to move the legs, occurring during inactivity and at night, when rest is most desired. RLS is clinically significant, especially when severe, as it causes sleep disturbance, and is associated with both depression and cardiovascular disease.[1–3] These associations are of interest to public health as RLS is a common disease, with a prevalence in North America and Europe between 5% and 10%.[4] Although the pathophysiology of RLS is not entirely clear, dysfunction in the A11 dopaminergic system and impaired brain iron homeostasis are likely important mechanisms underlying this troublesome disease.[5,6]

RLS is classified among the sleep-related movement disorders, even though abnormal movement is neither necessary nor sufficient to diagnose this condition. Despite this, abnormal movements do occur in the form of periodic limb movements during sleep (PLMS) in as many as 90% of RLS sufferers.[1] PLMS consist of brisk foot and knee flexive movements, occurring every 20–40 seconds during sleep.[7] Without considering these movements, the diagnosis of RLS is made on the basis of the presence, timing, and characteristics of subjective symptoms, and the absence of conditions that can "mimic" RLS.[8,9] Because diagnosis of RLS is based on historical symptoms, both sensitivity and specificity are largely variable depending on the experience and knowledge of the practitioner retrieving this information. Therefore, in clinical practice, where there are practitioners of varying levels of experience, misdiagnosis of RLS is common (author's experience).

When considering screening for RLS in research, an interview is often replaced by a questionnaire that screens for RLS. The use of a questionnaire eliminates the factor of interviewer experience and knowledge, but adds variability in that questions often differ from one questionnaire to the next. This issue of questionnaire variability is very problematic when trying to make inferences across different epidemiologic studies that have estimated RLS prevalence.[10] Thus, current

methods used to diagnose RLS in both clinical and investigational settings, are tool- and operator dependent, compromising both sensitivity and specificity.

In addition to occurring in the majority of patients with RLS, PLMS and their frequency correlate with the severity of RLS and respond to medical treatment similarly to the sensory symptoms of RLS, arguing for shared pathophysiology.[11,12] The purpose of this monograph is to briefly outline common pitfalls in the diagnosis of RLS, then to describe important adjoining features of RLS and PLMS in areas of pathophysiology, genetics, pharmacology, epidemiology, and clinical relevance, and finally to make an argument for the inclusion of PLMS measurement in the diagnosis of RLS.

Pitfalls in RLS diagnosis

In 2003, the International RLS Study Group (IRLSSG) published the minimum criteria necessary to diagnose RLS, which included 1) an urge to move the legs, usually accompanied by uncomfortable sensations, 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, 3) the urge to move or unpleasant sensations are partially or completely relieved by movement, and 4) worsening of symptoms in the evening or night.[13] In 2014, these criteria were amended to include a fifth essential criterion, differential diagnosis, to decrease the chances that RLS symptoms would be confused with similar symptoms from other conditions (Table 1).[8] In fact, the need to differentiate RLS from entities that can mimic RLS is likely the biggest pitfall of RLS diagnosis, as the ability to do so depends highly on the experience of the information retriever, not only with RLS itself, but with other conditions that mimic RLS, including peripheral neuropathy and nocturnal leg cramps. So the specificity of RLS diagnosis is likely to vary greatly among different operators, depending on experience and the inquisitiveness to ask about other conditions. Clearly, experience varies greatly in the clinical realm where practitioners have varying years of experience, types of education (physician vs. nurse), and areas of expertise (neurologist vs. internist). In research, RLS screening is often conducted by "trained" research assistants who may have no specific training in diagnosing conditions that may mimic RLS.

The diagnosis of RLS is contingent on an accurate and clear description or history. Inherently, sensations associated with RLS symptoms are difficult to describe, often making this a challenge for patients. Still, patients must be able to articulate symptoms and should be asked to describe the RLS symptoms in their own words. The ability to accurately characterize symptoms clearly differs among patients, and this variation compromises both specificity and sensitivity.

RLS can also be diagnosed by questionnaire. The advantage of using a questionnaire to diagnose RLS is that operator experience is no longer an issue. The four core RLS criteria can easily be formatted into a questionnaire, and, to date, this is the most common means by which RLS has been determined in epidemiologic studies to estimate prevalence.[10] Unfortunately, across studies, the wording of these questions has varied, and, at times, the four criteria have been screened in three or fewer questions.[14,15] Furthermore, questions to rule out RLS mimics have scarcely been used. There is only one validated questionnaire that includes IRLSSG criteria and items that screen for RLS mimics: the Cambridge–Hopkins RLS questionnaire.[16]

In sum, these pitfalls negatively affect both sensitivity and specificity in accurately diagnosing RLS, the main problem being specificity. The addition of an objective-qualifying criterion, such as the presence of PLMS, would help to increase specificity in the diagnosis of RLS.

Interconnected pathophysiology?

Although definitive pathophysiologic mechanisms have not been elucidated for either RLS or PLMS, preliminary work suggests that these two entities share common pathophysiologic origins. PLMS are seen in 80–90% of persons with RLS.[1] While awake, periodic movements are often preceded by sensory discomfort or an urge to move, and both involuntary movement and sensory discomfort can be aborted if voluntary movement (e.g., walking) occurs.[17]

PLMS are thought to arise from a spinal generator as affected muscles are activated in a rostral to caudal or caudal to rostral fashion (e.g., L4→L5→S1 or S1→L5→L4).[17] Dopaminergic A11 neurons originating in the hypothalamus and projecting throughout the spinal cord have been implicated in animal models of RLS.[5,18] Neurons in this dopaminergic A11 system synapse in thalamic nuclei before eventually projecting to the spinal cord.[19] The medial thalamus has been implicated as an important structure in the pathogenesis of RLS, showing decreased connectivity and reduced metabolism in functional imaging studies.[20,21] These studies suggest that the symptoms of RLS may evolve into the movements of PLMS through a diencephalic disinhibition phenomenon, which activates a spinal movement generator.

Pharmacology

Dopaminergic dysfunction may underlie both RLS and PLMS. Similarity in the neuro-chemical basis of RLS and PLMS is supported by the pharmacology of these two entities. It has been known for some time that dopamine agonist medication effectively treats the symptoms of RLS.[24] In addition to ameliorating the sensory discomfort of RLS, dopamine agonists significantly decrease the number of PLMS observed at night and can even reduce PLMS when RLS is not present (such as PLMS in narcolepsy).[25,26] Drugs that preferentially target the D3 receptor subtype, including pramipexole, compared with those that target the D2 receptor subtype, bromocriptine, have greater efficacy in reducing both RLS symptoms and PLMS.[27]

PLMS seem to arise or become more frequent with the use of many antidepressant medications, including tricyclic antidepressants, fluoxetine, and venlafaxine but not buproprion.[28,29] Similarly, antidepressant medications can worsen the severity of RLS symptoms, again arguing for shared pharmacology and thus pathophysiology of RLS and PLMS.[30]

Genetics

Genome-wide association studies have identified that RLS is associated with genetic variants or single nucleotide polymorphisms

Table 1. International Restless Legs Syndrome Study Group Consensus Diagnostic Criteria for RLS

1) An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.
2) The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3) The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4) The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night rather than during the day.
5) The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).
A. Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year.
B. Intermittent RLS/WED: symptoms when not treated would occur on average

Abbreviations: RLS, Restless Legs Syndrome; WED, Willis Ekbom Disease.

on the following genes: BTBD9 on chromosome 6, MEIS1 on chromosome 2, mitogen-activated protein kinase kinase 5 (MAP2K5)/Ladybird Homeobox Co-repressor 1 (LBXCOR1) on chromosome 15, and protein tyrosine phosphatase, receptor type, D (PTPRD) on chromosome 9.[31–33] The function of these genes is mainly related to embryonic neuronal development, but how they relate to RLS or PLMS is not known. Interestingly, in an Icelandic population, Stefansson et al. found that there was a significant association between an intronic variant on BTBD9 and having both RLS and PLMS.[31] This association was present in persons who were PLMS positive and RLS negative, but not RLS positive and PLMS negative, suggesting that there was greater genetic association with PLMS rather than RLS. More recent work has shown that variants within TOX3/BC034767, MEIS1 (two unlinked loci), MAP2K5/SKOR1, and PTPRD as well as BTBD9 are significantly associated with the presence of PLMS, and that this association is only modestly reduced when adjusting for the presence of RLS symptoms.[34]

Epidemiology

There are similarities in prevalence between RLS and PLMS, with estimates of between 5% and 11% in the general population for both entities.[4,35,36] Prevalence of RLS has been evaluated in over 25 countries in more than 50 different epidemiologic studies.[10] Far fewer studies have estimated the prevalence of PLMS, even though there is significant crossover of these two entities clinically. PLMS are seen in up to 90% of persons with RLS, but they also occur in the absence of RLS and are associated with other disorders, including sleep apnea, stroke, and hypertension.[1,37–39]

In a sample of randomly chosen adults between the ages of 18 and 65 years, 7.6% of 592 individuals had PLMS recorded by polysomnography (PSG). Interestingly, PLMS were significantly more common in Caucasians than African Americans (9.3% vs. 4.3%).[40] The prevalence of PLMS seems to increase in elderly people, as 45% of 427 elderly people over 65 years were found to have PLMS on PSG; a similar number of persons with PLMS was found in a community-dwelling elderly female population.[41,42] On the other hand, RLS may begin at any age, but usually begins after the age of 40 years.[43] Similar to PLMS, RLS is most prevalent between the ages of 60 and 79 years.[4]

The prevalence of RLS is higher as PLMS frequency increases with advancing age in RLS after the age of 15 and then again after age 65.[7] There are conflicting data when considering the correlation between PLMS frequency and severity of RLS, but, generally, PLMS frequency is thought to increase as severity of RLS worsens.[44] These similarities in the epidemiology of RLS and PLMS further strengthen the rationale to include PLMS measurement in the diagnosis of RLS.

Clinical relevance

The clinical relevance of RLS is far-reaching, affecting different areas relevant to health. RLS often prevents the onset of sleep and is commonly associated with insomnia.[4] Sleep fragmentation consisting of recurrent arousal from sleep is also commonly associated with RLS.[1] This sleep disruption may be the basis for the increased prevalence of depression in persons with RLS, in whom the odds of having depression is increased more than two-and-a-half-fold compared to the general population.[45] Finally, there is growing interest in the potential increased cardiovascular risk in persons with RLS. From two large sleep epidemiology studies, frequent and severe RLS was associated with a greater than twofold increased odds of prevalent cardiovascular disease, which included myocardial infarction, angina, and having had coronary revascularization.[2,3] Some but not all longitudinal studies have confirmed this relationship between RLS and incident cardiovascular disease.[46–48]

Clinical associations with PLMS seem to mirror those for RLS. Like in RLS, sleep disruption associated with PLMS is well described. It is

common for arousal and limb movements to co-occur in a complex, whereby PLMS may either precede or follow arousal.[49,50] In addition to their association with arousal, PLMS also coincide with discrete surges in heart rate and blood pressure.[51] These surges reach the order of 20–30 mmHg for systolic blood pressure and 10 beats per minute for heart rate, and occur with PLMS in both persons with RLS and persons without RLS.[51,52] These surges in blood pressure may underlie the association (albeit not universally found) between RLS and hypertension.[53] In addition to these intermittent surges in blood pressure, PLMS have recently been linked to diurnal hypertension.[39] Like RLS, PLMS, especially when occurring with arousal, are associated with incident cardiovascular disease.[54] These findings suggest that PLMS are the substrate which relates RLS to the clinical entities of sleep disruption and cardiovascular disease.

Measurement of PLMS

PLMS consist of stereotypic movements made up of foot dorsi- and plantar flexion to a greater extent than flexion–extension at the knee.[55] Reflecting this pattern of movement, muscles involved in descending order of frequency in PLMS are tibialis anterior, gastrocnemius, biceps femoris, and rectus femoris. Rarely, arms are involved. Typically, PLMS are detected by electromyography (EMG) during a sleep study or PSG. In an in-laboratory sleep study, bilateral tibialis anterior EMG electrodes are included as part of the standard montage. Using this technology, PLMS appear as discrete, 0.5–5-second EMG bursts that occur approximately every 20–40 seconds (Figure 1). Although PLMS can be detected by EMG during overnight sleep study, the determination of whether or not an individual has PLMS is not an indication for PSG. So what are the other means by which PLMS can be detected and measured?

Different sensors have been used to detect PLMS. Piezoelectric sensors convert the energy of pressure differentials or acceleration into an electrical signal. Piezoelectric sensors, placed around the anterior tibialis, can be used to detect and measure PLMS. This sensor has been used as part of a PSG montage to measure PLMS.[54] But using this sensor does not circumvent the problem of PSG not being indicated to measure PLMS. Acceleration can also be detected using an accelerometer. Accelerometry is the basis for a PLMS detection device called the PAM-RL (Philips-Respironics, Murrysville, PA). The PAM-RL device is worn on either one or both ankles, and records movement data over several hours or even days. Raw movement data can then be autoscored with software to determine the presence and frequency of PLMS.

Discussion

It is important to note that this subject of the utility of including PLMS to increase specificity and sensitivity of RLS diagnosis has been studied previously. Using expert diagnosis of RLS based upon IRLSSG criteria as the gold standard, Benes et al.[56] determined the additional predictive value of using different ancillary features of RLS. By adding PLMS to IRLSSG criteria, an additional 10% of the diagnostic variance was explained, compared with 19% for the response to dopaminergic medication and 0.7% for RLS family history.[56] In other words, PLMS can aid in making the diagnosis of RLS, largely by increasing specificity.

Table 2 summarizes similarities shared between RLS and PLMS. In summary, PLMS are seen in 80–90% of persons with RLS, but their presence is neither sufficient nor necessary to diagnose RLS. In this monograph, shared features of RLS and PLMS that span different areas, including pathophysiology, genetics, pharmacology, and epidemiology, have been described. Since PLMS are measurable or objective, their inclusion among the diagnostic criteria of RLS, which are completely subjective, would be complementary. In RLS diagnosis, the issue of distinguishing the RLS mimic from RLS creates the most confusion, and including PLMS in the RLS definition could help to increase specificity. We, therefore, propose that PLMS be added as a supplementary criterion for the diagnosis of RLS, so that when the diagnosis is made on the basis of clinical symptomatology plus PLMS that the designation be electro-clinical RLS.

This new designation of electro-clinical RLS is not intended to replace the current diagnostic scheme. Nor is it advocated that RLS not be diagnosed when PLMS are not assessed. The assessment for

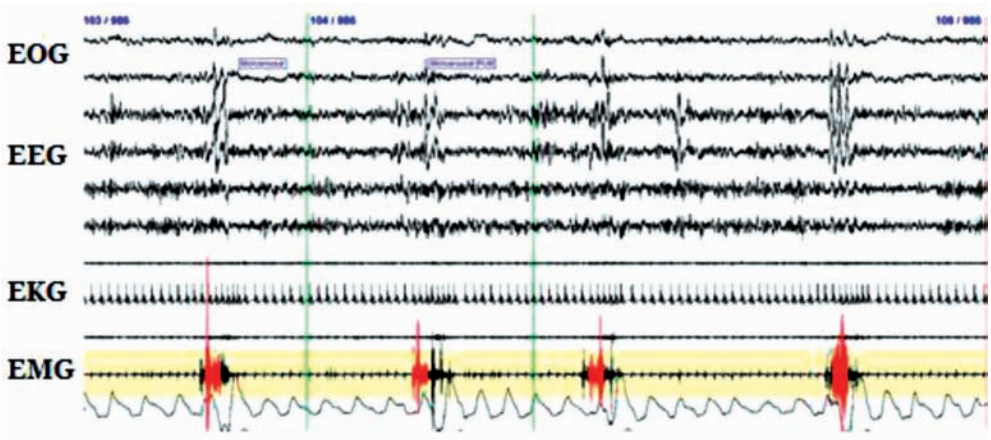

Figure 1. Periodic Limb Movements during Sleep. Pictured is a 2-minute epoch that shows periodic limb movements during sleep (PLMS), which occur every 20–30 seconds. Electroencephalographic activations and accelerations in heart rate occur at the same time as PLMS.

Table 2. Similarities between Restless Legs Syndrome and Periodic Limb Movements during Sleep

	Restless Legs Syndrome	Periodic Limb Movements During Sleep
Pathophysiology	• Possibly involvement of A11 dopaminergic system, which is located in the spinal cord.[19] • Decreased dopamine-2 receptor expression in putamen.[22]	• Emerge likely spinal cord generator as evidenced by pattern of recruitment of muscles, which is rostral to caudal or caudal to rostral in lumbar and sacral myotomes.[17] • Decreased urinary dopamine.[23]
Pharmacology	• Symptoms of RLS are decreased by dopamine agonists.[24] • D3-receptor agonists more effective than D2-receptor agonists.[27] • Symptom worsening by antidepressants.[30]	• PLMS are decreased by dopamine agonists.[25,26] • D3-receptor agonists more effective than D2-receptor agonists.[27] • PLMS become more frequent with antidepressants.[28]
Genetics	• Associated with BTBD9.[31] • TOX3/BC034767.[32] • MEIS1.[32] • MAP2K5/SKOR1.[32] • PTPRD.[33]	• Associated with BTBD9.[31] • TOX3/BC034767.[34] • MEIS1.[34] • MAP2K5/SKOR1.[34] • PTPRD.[34]
Epidemiology	• Around 10% prevalence.[36] • More common in older individuals	• Around 10% prevalence.[4] • More common in older individuals

Abbreviations: MAP2KD, Mitogen-Activated Protein Kinase Kinase 5; PLMS, Periodic Limb Movements during Sleep; PTPRD, Protein Tyrosine Phosphatase Receptor Type D; RLS, Restless Legs Syndrome.

PLMS alone without concern for sleep-disordered breathing should not prompt a nocturnal PSG. We also realize that different technologies used to determine PLMS can be expensive, available only in specialized centers, and are not available in areas or countries where sleep medicine is underdeveloped. But, the addition of PLMS as a supplementary criterion could be useful in cases where diagnosis is unclear, or in research projects where proper diagnosis is desired at the investigational level.

References

1. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. *Mov Disord* 1997;12:61–65. doi: http://dx.doi.org/10.1002/mds.870120111

2. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* 2006;7:545–552. doi: http://dx.doi.org/10.1016/j.sleep.2006.01.004

3. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* 2008;70:35–42. doi: http://dx.doi.org/10.1212/01.wnl.0000287072.93277.c9

4. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286–1292. doi: http://dx.doi.org/10.1001/archinte.165.11.1286

5. Ondo WG, He Y, Rajasekaran S, Le WD. Clinical correlates of 6-hydroxydopamine injections into A11 dopaminergic neurons in rats: A possible model for restless legs syndrome. *Mov Disord* 2000;15:154–158. doi: http://dx.doi.org/10.1002/1531-8257(200001)15:13.0.CO;2-Q

6. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* 2003;61:304–309. doi: http://dx.doi.org/10.1212/01.WNL.0000078887.16593.12

7. Ferri R, Manconi M, Lanuzza B, et al. Age-related changes in periodic leg movements during sleep in patients with restless legs syndrome. *Sleep Med* 2008;9:790–798. doi: http://dx.doi.org/10.1016/j.sleep.2007.08.020

8. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med* 2014;15:860–873. doi: http://dx.doi.org/10.1016/j.sleep.2014.03.025

9. Medicine AAoS. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

10. Koo BB. Restless legs syndrome: Relationship between prevalence and latitude. *Sleep Breath* 2012;16:1237–1245. doi: http://dx.doi.org/10.1007/s11325-011-0640-8

11. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res* 2002;53:547–554. doi: http://dx.doi.org/10.1016/S0022-3999(02)00443-9

12. Manconi M, Ferri R, Zucconi M, et al. First night efficacy of pramipexole in restless legs syndrome and periodic leg movements. *Sleep Med* 2007;8:491–497. doi: http://dx.doi.org/10.1016/j.sleep.2006.10.008

13. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–119. doi: http://dx.doi.org/10.1016/S1389-9457(03)00010-8

14. Happe S, Vennemann M, Evers S, Berger K. Treatment wish of individuals with known and unknown restless legs syndrome in the community. *J Neurol* 2008;255:1365–1371. doi: http://dx.doi.org/10.1007/s00415-008-0922-7

15. Gao X, Schwarzschild MA, Wang H, Ascherio A. Obesity and restless legs syndrome in men and women. *Neurology* 2009;72:1255–1261. doi: http://dx.doi.org/10.1212/01.wnl.0000345673.35676.1c

16. Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. *Sleep Med* 2009;10:1097–1100. doi: http://dx.doi.org/10.1016/j.sleep.2008.10.007

17. Trenkwalder C, Bucher SF, Oertel WH. Electrophysiological pattern of involuntary limb movements in the restless legs syndrome. *Muscle Nerve* 1996;19:155–162. doi: http://dx.doi.org/10.1002/(SICI)1097-4598(199602)19:23.0.CO;2-D

18. Qu S, Le W, Zhang X, Xie W, Zhang A, Ondo WG. Locomotion is increased in a11-lesioned mice with iron deprivation: A possible animal model for restless legs syndrome. *J Neuropathol Exp Neurol* 2007;66:383–388. doi: http://dx.doi.org/10.1097/nen.0b013e3180517b5f

19. Takada M, Li ZK, Hattori T. Single thalamic dopaminergic neurons project to both the neocortex and spinal cord. *Brain Res* 1988;455:346–352. doi: http://dx.doi.org/10.1016/0006-8993(88)90093-5

20. Rizzo G, Tonon C, Testa C, et al. Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. *Brain* 2012;135:3712–3720. doi: http://dx.doi.org/10.1093/brain/aws266

21. Ku J, Cho YW, Lee YS, et al. Functional connectivity alternation of the thalamus in restless legs syndrome patients during the asymptomatic period: A resting-state connectivity study using functional magnetic resonance imaging. *Sleep Med* 2014;15:289–294. doi: http://dx.doi.org/10.1016/j.sleep.2013.09.030

22. Connor JR, Wang XS, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain* 2009;132:2403–2412. doi: http://dx.doi.org/10.1093/brain/awp125

23. Cohrs S, Guan Z, Pohlmann K, et al. Nocturnal urinary dopamine excretion is reduced in otherwise healthy subjects with periodic leg movements in sleep. *Neurosci Lett* 2004;360:161–164. doi: http://dx.doi.org/10.1016/j.neulet.2004.02.056

24. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic movements in sleep: Physiopathology and treatment with L-dopa. *Clin Neuropharmacol* 1986;9:456–463. doi: http://dx.doi.org/10.1097/00002826-198610000-00006

25. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: A double-blind randomized trial. *Neurology* 1999;52:938–943. doi: http://dx.doi.org/10.1212/WNL.52.5.938

26. Boivin DB, Lorrain D, Montplaisir J. Effects of bromocriptine on periodic limb movements in human narcolepsy. *Neurology* 1993;43:2134–2136. doi: http://dx.doi.org/10.1212/WNL.43.10.2134

27. Manconi M, Ferri R, Zucconi M, et al. Preferential D2 or preferential D3 dopamine agonists in restless legs syndrome. *Neurology* 2011;77:110–117. doi: http://dx.doi.org/10.1212/WNL.0b013e3182242d91

28. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. *J Clin Psychiatry* 1997;58:348–350. doi: http://dx.doi.org/10.4088/JCP.v58n0803

29. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. *Biol Psychiatry* 2005;58:510–514. doi: http://dx.doi.org/10.1016/j.biopsych.2005.04.022

30. Rottach KG, Schaner BM, Kirch MH, et al. Restless legs syndrome as side effect of second generation antidepressants. *J Psychiatr Res* 2008;43:70–75. doi: http://dx.doi.org/10.1016/j.jpsychires.2008.02.006

31. Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. *N Engl J Med* 2007;357:639–647. doi: http://dx.doi.org/10.1056/NEJMoa072743

32. Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nat Genet* 2007;39:1000–1006. doi: http://dx.doi.org/10.1038/ng2099

33. Schormair B, Kemlink D, Roeske D, et al. PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. *Nat Genet* 2008;40:946–968. doi: http://dx.doi.org/10.1038/ng.190

34. Moore Ht, Winkelmann J, Lin L, Finn L, Peppard P, Mignot E. Periodic leg movements during sleep are associated with polymorphisms in BTBD9, TOX3/BC034767, MEIS1, MAP2K5/SKOR1, and PTPRD. *Sleep* 2014;37:1535–1542. doi: http://dx.doi.org/10.5665/sleep.4006

35. Kales A, Wilson T, Kales JD, et al. Measurements of all-night sleep in normal elderly persons: Effects of aging. *J Am Geriatr Soc* 1967;15:405–414. doi: http://dx.doi.org/10.1111/j.1532-5415.1967.tb02072.x

36. Bixler EO, Kales A, Vela-Bueno A, Jacoby JA, Scarone S, Soldatos CR. Nocturnal myoclonus and nocturnal myoclonic activity in the normal population. *Res Commun Chem Pathol Pharmacol* 1982;36:129–140.

37. Warnes H, Dinner DS, Kotagal P, Burgess RC. Periodic limb movements and sleep apnoea. *J Sleep Res* 1993;2:38–44. doi: http://dx.doi.org/10.1111/j.1365-2869.1993.tb00059.x

38. Kang SY, Sohn YH, Lee IK, Kim JS. Unilateral periodic limb movement in sleep after supratentorial cerebral infarction. *Parkinsonism Relat Disord* 2004;10:429–431. doi: http://dx.doi.org/10.1016/j.parkreldis.2004.04.009

39. Koo BB, Sillau S, Dean DA, 2nd, Lutsey PL, Redline S. Periodic limb movements during sleep and prevalent hypertension in the multi-ethnic study of

atherosclerosis. *Hypertension* 2015;65:70–77. doi: http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.04193

40. Scofield H, Roth T, Drake C. Periodic limb movements during sleep: Population prevalence, clinical correlates, and racial differences. *Sleep* 2008;31:1221–1227.

41. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Periodic limb movements in sleep in community-dwelling elderly. *Sleep* 1991;14:496–500.

42. Claman DM, Redline S, Blackwell T, et al. Prevalence and correlates of periodic limb movements in older women. *J Clin Sleep Med* 2006;2:438–445.

43. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: A synthesis of the literature. *Sleep Med Rev* 2012;16:283–295. doi: http://dx.doi.org/10.1016/j.smrv.2011.05.002

44. Garcia-Borreguero D, Larrosa O, de la Llave Y, Granizo JJ, Allen R. Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. *Sleep Med* 2004;5:561–565. doi: http://dx.doi.org/10.1016/j.sleep.2004.08.003

45. Winkelmann J, Prager M, Lieb R, et al. "Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* 2005;252:67–71. doi: http://dx.doi.org/10.1007/s00415-005-0604-7

46. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation* 2012;126:1689–1694. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.112.112698

47. Winter AC, Schurks M, Glynn RJ, et al. Restless legs syndrome and risk of incident cardiovascular disease in women and men: Prospective cohort study. *BMJ Open* 2012;2:e000866. doi: http://dx.doi.org/10.1136/bmjopen-2012-000866

48. Winter AC, Berger K, Glynn RJ, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. *Am J Med* 2013;126:228–235, 35.e1–e2.

49. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): Acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol* 2001;11:153–161. doi: http://dx.doi.org/10.1016/S0924-977X(01)00080-3

50. Ferri R, Rundo F, Zucconi M, et al. An evidence-based analysis of the association between periodic leg movements during sleep and arousals in restless legs syndrome. Sleep 2015 Jan 12.

51. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology* 2007;68:1213–1218. doi: http://dx.doi.org/10.1212/01.wnl.0000259036.89411.52

52. Pennestri MH, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. *Sleep Med* 2013;14:555–561. doi: http://dx.doi.org/10.1016/j.sleep.2013.02.005

53. Walters AS, Rye DB. Evidence continues to mount on the relationship of restless legs syndrome/ periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. *Sleep* 2010;33:287.

54. Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: Outcomes of sleep disorders in older men (MrOS) study. *Circulation* 2011;124:1223–1231. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.111.038968

55. Provini F, Vetrugno R, Meletti S, et al. Motor pattern of periodic limb movements during sleep. *Neurology* 2001;57:300–304. doi: http://dx.doi.org/10.1212/WNL.57.2.300

56. Benes H, von Eye A, Kohnen R. Empirical evaluation of the accuracy of diagnostic criteria for restless legs syndrome. *Sleep Med* 2009;10:524–530. doi: http://dx.doi.org/10.1016/j.sleep.2008.06.007